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TITLE: Dietary Fat and Vitamin E in Prostate Cancer Risk Among African Americans and West Africans: A Case-Control Study

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13. ABSTRACT (Maximum 200 Words)

The role of dietary fat and vitamin E in prostate cancer risk among African-Americans, African migrants and Africans is being investigated using a dietary assessment tool and by measuring plasma fatty acids and vitamin E in cases and controls. The FFQ appropriate for all three populations has been developed and continues to be in use for the Nigerian population. The BLOCK FFQ will be used for the Nashville population to allow for micronutrient analysis.

Nashville site: Administrative process including grant transfer, IRB approval, research assistant hire, design of souvenirs, posters and brochures has been completed, and purchase of supplies is in progress and community network and outreach has been initiated.

Nigeria Site: 52 potential cases have been recruited from urology and surgical clinics of the study hospitals and 42 potential controls have been recruited from the community.

Data management: The research assistant has been trained to manage the study data. The demographic section for 94 new, dietary assessment for 600 old and new, fatty acid laboratory report for 162 participants have been entered.

One manuscript has been published, a second is being revised, two talks and two abstracts have been presented from this study

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Table of Contents

INTRODUCTION:

[Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.]

This pilot study is designed to compare African American men in the Nashville area with African men living in Nigeria. It is designed as a second part to the study that accrued African men from Nigeria and African migrants and African Americans who live in the Washington metropolitan area between 2000 and 2002. The main objective of the study is to locate prostate cancer cases and select community based controls matched for age, socio-economic status and country of origin such that both groups will be compared with relation to their dietary risk factors for prostate cancer. The specific nutrients of interest are vitamin E, a protective antioxidant and essential fatty acids some of which have been proposed as risk factors for prostate carcinogenesis. Food items of interest that we hope to investigate include diary products, dietary supplements, fruits, vegetables, meat and fish.

BODY:

*[This section of the report shall describe the research accomplishments associated with each task outlined in the **approved** Statement Of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Appended publications and/or presentations **may** be substituted for detailed descriptions but **must** be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work **must** be approved by the Grants Officer. This approval must be obtained prior to initiating any change to the original Statement of Work.]*

Statement of Work:

Task 1

Hire research assistant. (1 – 3 months)

Identify phlebotomist / laboratory assistant in the Metro General Hospital to work on this study part-time.

The position of research assistant (RA) was published on the Meharry Medical College web page and a panel that included the PI, Dr. Malin and an administrative officer interviewed nine applicants over a period of two months. Angelica Keng, an experienced scientist with a Masters degree in public health, accepted to take up this position and started work on October 4th. 2004. We intend to encourage her to use this opportunity to extend her research experience, understand this particular research project and begin to plan a career in prostate cancer research. She completed training and is currently entering data collected over the past period. We plan data collection and sample handling training starting from March 2005.

The director of the Clinical Research Center at Meharry Medical College, Dr. Grandison, was contacted and he has assigned a research nurse in that unit to carry out all study phlebotomy services. Since we plan to draw fasting blood samples our participants will be included in her 8.00am schedule slot.

Task 2

Start-Up Phase and Plan Development (1 – 3 months)

-Urologists:

Drs. Joseph Smith, Michael Cookson of Vanderbilt University, and Ernest Smith of Meharry Medical College have accepted to work with us. We also have contacted the urology department of the Veterans hospital and they too are cooperative. In view of the fact that colleagues from Vanderbilt University are also recruiting similar study participants we also contacted the PI, Dr. Jay Fowke, and we shall be working collaboratively.

-Network Listing:

We have acquired a directory of African American churches in Nashville and have commenced the development of a listing of contact persons within the community who are willing to help with community networking. Only initial contact with 6 representatives of churches have been made at this time. A research associate in the department of surgery Marian Ladipo, MPH, will be working with my RA to compile a comprehensive networking list. They have received directives to develop a comprehensive community network list including local newspapers, radio and television stations, work sites etc. quidance

-The PI has secured the cooperation of key personnel at the Tennessee department of health, including the director of health, one of their senior epidemiologist (Rhonda BeLue, Ph.D.) and the cancer registrar George Lobdell who will also be resourceful links to the community.

Task 3

Training: PI and Research Assistant (2 – 4 months)

-The RA has completed training in the area of research ethics, human subject protection, and can process Institutional Review Board applications and obtain signed informed consent from participants.
-The RA has been trained to make professional initial telephone contacts to secure participants cooperation and to schedule study visits but has not conducted the test procedure here in Nashville.
-The RA has been trained on 2 of 3 study instruments and yet to be trained on the food frequency questionnaire.
-The RA will be trained in the handling, labeling, storage and shipping of research samples and the follow through of results and communicating and mailing results to participants before we begin to accrue participants in Nashville. This will take place in the last week of February 2005.
-We shall be scheduling the training to abstract information from medical records at a later date.

Task 4.

Subject Recruitment and Data Collection in the US. (4 – 24 months)

Nashville, TN:
Study supplies have been ordered and study brochures and flyers have been printed. Study souvenirs, pens, T-shirts and caps, have been received and we await the supply of blood draw supplies from a local distributor and the food frequency questionnaire from BLOCK. Advertisement will commence once we have all our supplies ready.

Nigeria Site:
Since we had a valid IRB approval for the Nigerian study we did not interrupt data collection at that site. So far we have received 4 packages (Blood samples, prostate biopsy paraffin blocks and pathology slides, completed questionnaires and Nigerian pathology reports) from Nigeria. Participant recruitment was carried out both in the community (n= 148) and at the hospital clinics (n=52).

Processing Pathology Samples: A pathologist, Dr. Marcia Wills, at the Vanderbilt University has been contacted and is willing to collaborate. Her role will include providing a second diagnostic opinion after preparing pathological slides from the biopsy paraffin block samples and providing histological reports.

Pathology samples:	2003	2004
EKU Hospital	43	34
Benin Hospital	33	18

Task 5.

Interim and On-going Data Analysis (3 - 24 months)

Data Enter:
A lot of progress has been made in this area since a full-time RA took over the task. The study questionnaire is in three main sections and the data is being entered in sections. There are now a total of 684 participants in the SPSS database, including data from the previous 355 participants from the Nigeria and Washington DC survey prior to and including 2003. The RA has now concentrating on cleaning the database and catching up with data entry. The database is made up of five main sections as shown below:

Sections	Previously Entered	Entered Current Period	Total
Personal Information	355	329	684
Dietary Assessment	146	304	450
Anthropometrics	355	222	577
Food Frequency	435	0	435
Free Fatty Acid	0	157	157

It is important to note that we are recruiting potential study participants and collecting information from 'potential cases', men with elevated PSA going for prostate biopsy, so that information is collected before they become diverted by the serious diagnosis of prostate cancer. The 'potential controls' pool will be available to select age/SES-matches for each confirmed case.

Fatty Acid Data:

Fatty acids were assayed in 2003 for a selected group of study participants from among the Africans in Nigeria, the African migrants in Washington DC and the African Americans in Washington DC and this data is now in the database.

	Controls	Elevated PSA	Total
Nigeria:	32	31	63
Washington DC:	37	57	94
Total	69	88	157

Data Analysis: Interim data analysis has led to the following manuscripts, abstracts and posters during the reporting period.

1. Publications:

F. Ukoli, U. Osime, F. Akereyeni, O. Okunzuwa, R. Kittles, L. Adams-Campbell. Prevalence of Elevated Serum Prostate Specific Antigen in Rural Nigeria. International Journal of Urology. 2003; 10:315-322.

Panguluri RC, Long LO, Chen W, Wang S, Coulibaly A, Ukoli F, Jackson A, Weinrich S, Ahaghotu C, Isaacs W, Kittles RA. COX-2 gene promoter haplotypes and prostate cancer risk. Carcinogenesis. 2004 Jan 30.

Kittles RA, Chen W, Pangulari RK, Ahaghotu C, Jackson A, Adebamowo CA, Griffin R, Williams T, Ukoli F, Adams-Campbell L, Kwagyan J, Isaacs W, Freeman V and Dunston GM. CYP3A4-V and prostate cancer in African Americans: causal or confounding association because of population stratification. Hum Genet. 2002, 110:553-560.

2. Poster Presentation:

Flora Ukoli, Chiledum Ahaghotu, Dionne Thorne, Augustine Mireku-Boateng, Aaron Jackson, Lucile Adams-Campbell. Screening for prostate cancer: Positive attitude and response by African American men. Presented at the Meharry/ Vanderbilt U54 Cancer Partnership Retreat. Nashville, TN. 2003.

3. Manuscript (Submitted):

Flora A. Ukoli, Eruke Egbagbe, Barbara B. Zhao, Efosa Iyamu, Dale Young, Philip Oside[3], Usifo Osime, Lucile L. Adams-Campbell. Anthropometric and body fat predictors of elevated PSA among rural and urban Nigerians: A population-based study. Submitted to Epidemiology, Biomarkers & Prevention. October 2004.

4. Oral Presentations:

Flora Ukoli. Community based prostate cancer dietary risk study: Recruiting African Americans and Africans through a screening program. Spring 2004 Seminar Series. North Carolina Central University, Durham, NC.

Flora Ukoli. Screening for prostate cancer: Positive attitude and response by African American men. Presented at the 18th Annual Howard University College of Medicine Resident/Faculty Scientific Research Forum. May 2003.

Flora Ukoli. Taking Control of Your Prostate Health: The Importance of Early Detection on Prostate Cancer. American Cancer Society "Let's Talk About It" Program. Washington DC. 2003.

5. Graduate Students Supervision:

a) Washington DC:

Mirza Baig, MBBS. Correlation of meat intake and serum PSA among urban African Men.

Syed Abdul Qadir Karim. MBBS, DTCD. Correlation of intake of fruits and vegetables and PSA levels in Nigerian men.

b) Nashville, TN. Meharry Medical College:

Emeka Amaefuna, M.D. The pattern of essential fatty acid profile among African-American and Nigerian men.

Esiri Esin, M.D. Tobacco and alcohol use pattern among Nigerians and African migrants living in the United States.

Task 6.

Report Writing and Presentations (18 - 24 months)

Data analysis and manuscript preparation.

1. Kittles RA, Chen W, Pangulari RK, Ahaghotu C, Jackson A, Adebamowo CA, Griffin R, Williams T, **Ukoli F**, Adams-Campbell L, Kwagyan J, Isaacs W, Freeman V and Dunston GM. CYP3A4-V and prostate cancer in African Americans: causal or confounding association because of population stratification. Hum Genet. 2002, 110:553-560.

2. Desai PP, Bunker CH, **Ukoli FA**, Kamboh MI.Genetic variation in the apolipoprotein D gene among African blacks and its significance in lipid metabolism. Atherosclerosis. 2002 Aug;163(2):329-38.

3. **F. Ukoli,** U. Osime, F. Akereyeni, O. Okunzuwa, R. Kittles, L. Adams-Campbell. Prevalence of Elevated Serum Prostate Specific Antigen in Rural Nigeria. International Journal of Urology. 2003; 10:315-322.

Abstracts:

4. Teresita Hernandez[1], PhD, Lora Wilder[1], ScD, RD, **Flora Ukoli[2],** MBBS, DPH, MPH, Johanna Dwyer[3], DSc, RD 1. The ABC's of instrument development for dietary assessment in diverse populations. *Affiliations*: [1]Health Technomics, Inc. Annandale, VA, [2]Howard University, Washington, DC, [3]Tufts University, Boston, MA. Presented at the American Society for Nutritional Science. Experimental Biology 2003 Conference. April 2003.

5. Teresita Hernández[1], PhD, Lora Wilder[1], ScD, and **Flora Ukoli[2]**, MBBS, MPH. ANALYZING INTAKES OF DIVERSE POPULATIONS: CHALLENGES IN SETTING UP A NIGERIAN FOOD DATABASE. *Affiliations:* [1]Health Technomics, Inc, Annandale, VA, [2]Howard University, Washington DC. Presented at the The International Food Data Conference. July 2003. Washington DC.

Presentation of results at seminars.

The PI is scheduled to present findings at an Epidemiology seminar at the Vanderbilt University and Grand round seminar at Meharry Medical College in 2005.

KEY RESEARCH ACCOMPLISHMENTS:
[Bulleted list of key research accomplishments emanating from this research.]

Nigerian Site:

1. Men with abnormal prostate cancer screening continue to be contacted and encouraged to visit their urologists and consider a prostate biopsy if indicated.
2. Men with elevated PSA seen at the urology clinics have gone on to have biopsies and received a diagnosis of prostate cancer. They are receiving usual medical as indicated.

Nashville Site:

1. Data entry accomplished.
2. Prepared to commence recruiting study participants.

REPORTABLE OUTCOMES:
[Provide a list of reportable outcomes that have resulted from this research to include:]

The study has met most of the set objectives for the first year:

1. Initiated partnership with some black communities in Nashville and continue to maintain partnership with 2 rural and 2 urban communities in Nigeria.

2. Initiated connection with existing community outreach core of other research programs at Meharry Medical College and Vanderbilt University

3. Included three urologists in Nigeria who have permitted the research team to approach their patients for possible participation in the study.

4. Identified urologists/family physicians in Nashville who have agreed to inform new cases about the study.

5. Collected demographic and dietary assessment information for 329 men.

6. Collected and stored plasma, serum, cell, clot and urine samples for laboratory analysis for 286 men.

7. Purchased study supplies including sample shipping packages and study souvenirs.

Challenges:

Nigerian Site:

1 Biopsy in Nigeria:
   a. Men without symptoms are still not accepting to undergo a prostate biopsy even in the light of elevated PSA.
   b. Biopsy is performed blindly (no ultrasound guided biopsy) and so the tissue collected is very small. The pathologist suggests the need to blindly collect 4-6 biopsy samples and this does require purchasing an ultrasound machine with a rectal probe for that site.

2 Mailing of diagnostic samples and study materials from Nigeria.
One out of 4 packages was not handled as expected leading to the loss of parts of the package sent through FedEx. The PI was able to trace and receive the package containing prostate biopsy blocks and slides but the package containing the study questionnaires for 29 participants was not located.
It is suspected that custom officers did not repack the shipment properly after inspection, leading to separation of parts of the shipment. It should be noted that the blood samples were intact and received as expected as the box was rightly labeled as diagnostic samples with the CDC import of diagnostic sample label.

3 Need to hire at least 2 doctors at the post-doctoral/resident level to work closely with the research team in the process of data collection. The doctors will require training and encouraged to develop interest in this research area so that they can act more like junior investigators and ensure data quality control. This will be accomplished during the PI's 3-week visit to Nigeria in February 2005.

Nashville Site:

1 Grant transfer process took approximately one year. During this period the PI was able to submit 3 grants and one of them was funded.

2 Recruitment of study participants will start in March, 2005. More attention will be placed on working with family physicians who may be in a better position to refer 'potential' cases to the study. By the time cases are conclusively diagnosed by the urologist both patient and urologist are more concerned with treatment plans rather than in research that does not bear direct benefits for their very serious condition. Recruitment at this point appears to be insensitive to the patients' needs.

CONCLUSIONS:

[Summarize the results to include the Importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.]

This is the first of a two-year pilot project and the important strategies have been put in place to meet the study accrual numbers in the next 12 months for the Nashville area. Collection of data in Nigeria started off very well within the community and has slowed down because they are currently recruiting 'potential' cases, which is a slower process than recruiting 'potential' controls. Training of research personnel should be repeated to ensure adherence to the study protocol. There will be need for more aggressive media exposure in Nashville local newspapers, newsletters, radio and television, in addition to submitting study flyer and a letter of introduction about the PI and the study in person to churches, family physicians, urologists and HMO so as to access both cancer and healthy population for the study.

REFERENCES: *[List all references pertinent to the report using a standard journal format (i.e. format used in Science, Military Medicine, etc.).]*

APPENDICES: *[Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.]*

BINDING: *[Because all reports are entered into the Department of Defense Technical Reports database collection and are microfiched, it is recommended that all reports be bound by stapling the pages together in the upper left hand corner. All original reports shall be legible and contain original photos/illustrations. Figures shall include figure legends and be clearly marked with figure numbers].*

Appendix:

Two manuscripts attached.

1) Title: Prevalence of Elevated Serum Prostate Specific Antigen in Rural Nigeria.

2) Title: Anthropometric and Body Fat Predictors of Elevated Prostate Specific Antigen among Rural and Urban Nigerians: A Population-Based Study

Prevalence of Elevated Serum Prostate Specific Antigen in Rural Nigeria.

Flora Ukoli,[a] Usifo Osime,[b] Folasade Akereyeni[b], Osazuwa Okunzuwa[c], Rick Kittles[a], Lucile Adams-Campbell[a].

[a]Howard University Cancer Center, Washington, D.C., U.S.A.

[b]Department of Surgery, University of Benin, Benin-City, Nigeria.

[c] Osse Health Clinic, Osse, Edo State, Nigeria.

SUMMARY

Background: Recent hospital and cancer registry data show increasing prostate cancer incidence in Nigeria previously regarded as a low incidence region. This study investigates the prevalence of prostate cancer risk in a previously unscreened cohort of rural Nigerians.

Methods: Rural Nigerian men, 40 years and older, were invited from home and screened by serum prostate specific antigen (PSA) and digital rectal examination (DRE) and those with PSA ≥ 4ng./ml. and/or abnormal DRE were referred for prostate biopsy.

Results: Of 200 consecutive men invited 151(75.5%) presented for screening, mean age 56.45± 15.1 and 95(61.6%) were ≥ 50 years. Of the 140 who allowed blood draw, PSA correlated with age, r=0.3, p<0.01, 14(10.0%) had abnormal PSA ≥ 4ng/ml., increasing from 3(3.6%) in men <60 years to 4(50%) in men ≥80 years. The rate was 13(15.7%) for men ≥50 years and there was no evidence of increased incidence of prostatitis in the community. Mean (median) PSA in ng./ml. increased from 1.17 (0.60) in the youngest to 13.75 (4.45) in the oldest cohort. Of those who accepted DRE 38(29.0%) had enlarged prostate, including 2 nodular prostate, one-third with symptoms, increasing from 4(5.4%) in those <50 years to 6(75.0%) in men ≥80 years. The proportion of men with PSA ≥ 4ng/ml among those with enlarged versus normal prostate is 27.0% to 3.4%, p<0.001, and the pattern was similar for men ≥60 years and those <60 years. The 40(32.0%) men referred for prostate

biopsy defaulted mainly because they did not fully understand the need for further investigation being symptom free or were afraid of the possible side effects of the procedure or the diagnosis of cancer.

Conclusion: The proportion of men with PSA ≥4ng/ml is comparable to that of previously unscreened populations with high incidence of prostate cancer such as African Americans. There is need to conduct a larger study to confirm these findings and to intensify efforts to determine the prostate cancer detection rate by biopsy in this population. A prostate cancer awareness and education campaign will be useful in this community.

Keywords: Prostate specific antigen, prostate cancer, digital rectal examination, Africa, Nigeria, Black.

INTRODUCTION:

Prostate cancer rates in African-Americans,[1,2] and Afro-Caribbean blacks[3] have been reported to be high, suggesting genetic predisposition. However only 10% of prostate cancers are due to the familial or genetic type while 90% are considered sporadic, due to the combination or interaction of environmental and genetic factors. Rates of latent prostate cancer are similar all over the world, while the prevalence of the aggressive form varies, emphasizing the importance of cancer promoting rather than cancer initiating environmental factors.[4]

Most reports from West African countries like Nigeria are descriptive hospital data reporting increasing incidence of prostate cancer.[5-8] The recently reported population incidence rate derived from cancer register data is 127/100,000 with a mean age 68.3 $\pm$ 9.4 years and a median age of 67.5 years[5,9]. From autopsy studies age adjusted incidence rate of invasive carcinoma was higher among African Americans than in Africans.[10] Some reasons for this finding may be incomplete detection of

cases that never presented in hospitals or those lost to follow-up on discharge and later died at home, lower life expectancy and selection bias for routine autopsies.

Developing countries like Nigeria now appear to be undergoing a *cancer epidemic* similar to that in developed countries. Reasons for the low incidence in the past could be due to under reporting and lack of adequate diagnosis. Although the impact of lifestyle changes have not been studied, increased smoking and alcohol use, dietary change to a mixture of traditional Nigerian and Western foods, consumption of foods with additives and increased use of processed beverages are proposed as possible risk factors.[11] Prostate cancer that was second only to liver cancer is presently the commonest cancer among men over 18 years with an increased relative frequency ratio of 13.2% in 1980-88 to 16.14% in 1989-96.[9] For valid international comparisons there is need for uniform standard of data collection and complete national health and census statistics. In the absence of such data this cross-sectional study investigates the pattern of PSA distribution in a defined rural West-African community in southern Nigeria in men 40 years and older. There are over 45 distinct ethnic groups in Nigeria and although people migrate all over the country there is a tendency for ethnic homogeneity in rural communities.

METHODS:

Selection of Study population:

This study was carried out in Edo state, southern Nigeria, in a rural community where 84.7% of the men interviewed are of the Edo tribe, the others are Urhobos, Itsekiris and Yorubas from the neighboring Delta state. All the men reported that their grandparents were Nigerians.

The first 200 men who were 40 years and older from consecutive houses/households in a rural Nigerian community, starting from the house of the village head, were informed about a health survey that would require a blood draw and digital rectal examination by a public health nurse who

resided in that village. Interested men who signed the consent form after reading or having it read to them were scheduled for a clinic visit. A conscious attempt was made at initial contact to use 'medical check-up', 'disease of the prostate', or 'conditions that affect urination in elderly men' rather than 'prostate cancer screening'. Those who did not consent immediately were given a copy of the consent form to read in their own time and to consult with family and friends and were asked to come to the local health center if they decided to participate. The study was approved by the IRB of Howard University, Washington DC, and by the Research Ethics Committee of the University of Benin Teaching Hospital, Nigeria.

Measures:

The questionnaire that included demographics, medical, dietary and family history of prostate and other cancers, history of tobacco and alcohol use and physical measurements was completed by trained interviewers. For men who did not have official birth records the interviewers crosschecked the self-declared age by adding age at first marriage, years before birth of first living child and age of first child in addition to using other historical milestones to check year of birth. A physician observing all precautions against transmission of blood borne pathogens collected 30ml of venous blood with a multiple draw vacutainer needle into three specimen tubes. The participants then had a digital rectal examination (DRE) by the study surgeon who has many years of urology experience and they also consulted him regarding problems with urination. The DRE was carried out with a lubricated gloved index finger with the patient lying on their side with both legs flexed, and the prostate size, presence of a sulcus, consistency and nodularity was recorded on a form.

The blood samples were centrifuged for 15 minutes after standing for a minimum of 30 minutes. Serum was then pipetted into 2ml. microvials, packed in cardboard storage boxes and transported on ice within 3 hours of collection to be stored in a freezer for up to three months until

transported on dry ice to Howard University laboratory where it was stored at –70 degrees. The microvials of serum were then sent to a registered commercial laboratory for PSA analysis by the microparticles enzyme immunoassay technology.[12]

Individual result sheets including follow-up recommendation were hand delivered to each participant by the community health nurse with detail explanation about their results. Those with abnormal results were encouraged to consult the doctor at the local health center for counseling. The doctor counseled them with regard further investigations and the need and safety of prostate biopsy before referral to the surgeon and urologist at the teaching hospital. Participants were informed that they will only pay the usual hospital fee and that they will not be charged for the biopsy procedure, histology report or antibiotics.

Statistical analysis:

The demographic, medical and other personal information were analyzed and summarized as frequency counts and percent. Mean and median PSA was calculated and compared across various sub-groups using the 2 sample independent t-test and the Mann-Whitney test respectively. PSA was summarized as grouped data classified into four levels, less than 2.5, 2.5-3.9, 4.0-9.9 and ≥10ng/ml. For statistical analysis by Chi-square test participants were dichotomized into two groups for PSA (<4ng/ml and ≥4ng/ml), two groups for DRE (normal and enlarged/abnormal) and two groups for age (<60 years and ≥60 years). All calculations were done by SPSS 8.0 windows version.

RESULTS:

Of 176(88.0%) men who consented, 151(85.7%) presented for the study. Five (3.3%) did not state their age, PSA for 11(7.3%) and DRE for 20(13.2%) were not available because of participant's refusal or rescheduling difficulty. Those who did not complete the survey were not demographically different from those who did. Eighty-five (56.3%) have lived in this rural town for

20 years or longer, 108(71.6%) were full-time or part-time farmers, 44(29.2%) were skilled and semi-skilled artisans, 16(10.6%) were teachers and administrative assistants, 7(4.6%) were senior administrators / businessmen and 10(6.6%) were retired. Their ages ranged from 40–110 years with a mean of 56.45±15.1 years and 95(61.6%) were ≥50 years.

Of the cigarette smokers 45(69.3%) smoked <5 cigarettes per day, 13(20.0%) smoked between 5-10 and 7(10.8%) smoked a pack or more per day. Of the 57(37.7%) who drank alcohol regularly 33(21.9%) drank more than 5 drinks at an occasion once in the last month; a drink of alcohol being 12ozs of beer, a glass of wine or a shot of liquor. Half of the men had <7 children while others had 7- 40 children as a result of polygamy and remarriage. Mean (median) PSA ng/ml increased from 1.17 (0.60) in the youngest to 13.75 (4.45) in the oldest age cohort (Table 1).

Of the 140 who allowed blood draw, PSA ranged from 0.1 to 64.8 ng/ml., 14(10.0%) had abnormal PSA ≥4ng/ml., increasing from 3(3.6%) in men <60 years to 4(50%) among men ≥80 years (Table 2). PSA correlated with age among those with normal and abnormal PSA, $r=0.3$, $p<0.01$ and $r=0.4$, $p<0.1$ respectively. Men ≥60 years had a higher proportion of abnormal PSA ≥4ng/ml compared to men < 60 years 20.8% vs. 3.6%, Chi-Square 10.3, $p<0.001$.

The rates for enlarged prostate with or without symptoms increased from 4(5.4%) in the youngest to 6(75.0%) in the oldest age group (Table 3). Men ≥60 years had a higher proportion of enlarged /abnormal prostate on DRE compared to the men <60 years, 49.0% vs. 16.5%, Chi-Square 15.9, $p<0.001$. More men with enlarged prostate gave a history of urinary problems compared to those with normal size prostate, 11(28.9%) vs. 7(7.5%), $p<0.004$. The respective rate for history of symptoms was 12(22.2%) vs. 6(6.8%), $p<0.01$, in men ≥60 compared to men <60 years. The proportion of men with PSA ≥4ng/ml was not statistically different for men with or without a history of urinary symptoms in both the younger and the older group, 1(16.7%) vs. 2(2.7%) and

8(20.5%) vs. 3(25%), respectively. The major urinary symptoms were frequency 5(27.8%), straining, difficulty or pain starting urination 5(27.8%), weak urinary stream 3(16.7%), urethritis 3(16.7%) and dribbling 2(11.1%). There was no report of symptoms suggestive of acute or chronic prostatitis.

Three (3.4%) men with normal prostate on DRE, 9(25.7%) with enlarged prostate, one with hard indurated prostate and one who refused DRE had abnormal PSA ≥ 4ng./ml, $p<0.001$ (Table 4). This pattern was similar for men <60 and those ≥60 years, Chi-Square 6.0, $p<0.015$ and Chi-Square 4.2, $p<0.04$ respectively. At least 40(32.0%) had abnormal PSA and/or DRE warranting referral for prostate biopsy. The mean (median) PSA ng/ml for men with enlarged prostate was statistically higher than that for men with normal prostate in both the younger and older cohort, 3.13 (1.40) to 1.05 (0.06), $p<0.01$ and 7.92 (2.60) to 2.19 (0.65), $p<0.01$, respectively.

DISCUSSION:

This study is one of the first to conduct prostate cancer 'case-finding' in a previously unscreened rural community in Nigeria using serum PSA as the biomarker in combination with DRE examination performed by an experienced surgeon. Apart from the small sample size a major limitation of this study is the lack of prostate biopsy follow-up information. That 40(32%) men have abnormal PSA and/or DRE is an important finding especially when 9(6.6%) of the men have a PSA over 10ng./ml. The men with abnormal PSA are yet to present for prostate biopsy primarily because they do not understand the need for the investigation especially when they are symptom free. There has been no public awareness campaign about prostate cancer in the country and having been told that the prostate is one of the male reproductive glands irrational fear of impotence resulting from any surgery or procedure in the ano-rectal region cannot be ruled out.

The situation however is different for a condition like breast cancer where awareness level has been raised by recent campaigns in Nigeria, the breast being more accessible for examination and biopsy, and the availability of the fine needle aspiration technique that is less invasive.[13] Until public awareness of the necessity and safety of prostate biopsy is raised enough for symptom free men to accept the procedure for diagnostic purposes, the rate for abnormal PSA will have to serve as a crude index of the prevalence of prostate cancer risk. A major assumption in this study is that the cutoff point of 4ng./ml. is appropriate for the population. PSA is known to increase with age and with the size of the prostate and values over 10ng/ml are suspicious of cancer regardless of age and prostate size. Even if ultrasound facility was easily available to this rural community PSA density has not been shown to have superior predictive value for prostate cancer over total PSA.

International comparison of percentage population at higher risk for prostate cancer from published literature is complicated by the differences in the age range included in PSA-based screenings and the PSA cutoff point above which the participant is classified as abnormal. The usual cutoff point in most studies is PSA ≥ 4ng/ml or PSA >4ng/ml. while fewer studies use PSA ≥10ng./ml. or PSA ≥2ng/ml. Studies can recruit a few hundreds or less as in single practice screenings or include thousands of men as in multi-center studies; from a one day screening to screenings that span several years. Regular or serial PSA-based prostate cancer screening over time will lead to a decrease in the proportion of men with abnormal test results, and the prostate cancer detection rate will also decrease to near the population-based incidence rate.[14] The proportion of men with abnormal PSA in this population-based screening will therefore be a prevalence rate as there had been no routine screening in the past.

In the last two decades population based PSA-based screenings in the US that included men 50 years and older reported abnormal PSA rates >4ng/ml. of 10.0% - 15.0%.[15-18] Reports from the

Netherlands[19] and Singapore[20] were similar but included people with PSA ≥4ng./ml. and rates from Germany[21] and Sweden[22] are 17.0-17.2%, prostate cancer detection rates ranged from 2.1% to 4.6%. In a South African study that included 4.5% black Africans, an abnormal PSA rate of 15.2% and a prostate cancer detection rate of 3.5% overall and 8.5% for black men was reported.[23] The prevalence of abnormal PSA ≥4ng./ml. in these Nigerian men, ≥50 years, is comparable at 15.7%. Including men 40 years upwards the rate is 10.0%, comparable to the 8% rate for slightly younger African Americans, mean age 55 years, in Detroit[24]. These rates are quite different from the lower rate of 3.4% with prostate cancer detection rate of 1.3% in Japan, using an ethnic specific PSA cutoff point of ≥2ng/ml to detect half of the cases.[25]

Other authors from Nigeria who conducted a hospital based study reported a very low rate of 1(1.7%) for abnormal PSA ≥4ng/ml among the controls who were aged 22-76 years and that no man younger than 50 years had a PSA >2 ng/ml.[26] In our study 5(9.4%) men below 50 years had a PSA >2ng/ml. This divergent finding is not surprising as controls recruited in an hospital setting are not representative of the general population and the inclusion of very young men under 40 years. However the rate of abnormal PSA among the men with clinical BPH in that study was 63% as compared to 50% for the men with enlarged prostate with symptoms in this study but 26% for all men with enlarged prostate. This disparity is also expected as our study included men with mild-moderate prostate enlargement, two-thirds without symptoms. The men in the referenced study had symptoms that warranted hospital visit suggestive or more severe prostate pathology.

The prostate cancer incidence rate of 127/100,000 for Nigeria,[5,9] histological evidence of prostate cancer in 14.8% of Nigerian patients with prostatism,[27] that prostate cancer has become the number one cancer in Nigerian men,[28] and an estimated age-adjusted prostate cancer incidence rate of 93.8/100,000 in Cameroon,[29] could be conservative rates as they have been derived from hospital

data and prostate cancer is a 'silent' disease that may not come to medical attention. However in Algeria prostate cancer is the fifteenth cancer among Arab men, and in Zimbabwe it is the fifth cancer in Africans but second cancer for Europeans.[30] Although cancer incidence data from Africa is sparse available information indicates a lot geographical variation. The few population based cancer registers in Africa who report incidence rate to the International Association of Cancer Registry (IARC) are not reliable because of inconsistency in data collection leading to poor data quality[13,30,31]. In comparison with other regions of the world, prostate cancer incidence per 100,000 in Africa, Senegal is 4.3 compared to 4.9 for Japan, 22.2 for Brazil and 100.2 for African Americans[31]. The Dakar Cancer Registry in Senegal was established in 1968.

The first cancer registry in Nigeria was founded in Ibadan in 1960, the Nigerian Cancer Society in 1968 and these bodies initiated the collection of cancer statistics among other objectives. In 1960 the crude cancer incidence rate for Ibadan, Nigeria, was 33.7 and 45.1 per 100,000 for males and females respectively.[11] Between 1960-80 prostate cancer was diagnosed third to non-Hodgkin's lymphoma and liver cancer. Cancer registration was incomplete because of lack of case notification. Registry staff actively collected data from different health institutions but records were unobtainable for a sizeable proportion of the population that tended to consult religious healers and traditional health practitioners.[13] Cancer registry data such as these will therefore under record prostate cancer because of its clinical and natural history.

While it is possible that the present increasing trend for prostate cancer in Nigeria is real, it may be as a result of improved detection from better availability and utilization of health facilities and the aging population. Environmental factors and race have been sited as significant contributors to the geographical variation in prostate cancer incidence. Cancer of the prostate is presently a frequently occurring cancer in Nigeria and the 15.7% rate of abnormal PSA in men 50 years and

older in this study population is cause for concern. It is therefore very important to secure histological diagnosis by prostate biopsy and investigate the appropriateness of using 4.0ng/ml as the cut-point for PSA abnormality. It will be worthwhile to also investigate the usefulness of 6-month repeat PSA or other tests such as percentage free prostate-specific antigen as additional screening tools to limit the sub-population that would require prostate biopsy.[32,33]

Prostate biopsy is a usual procedure in urology clinics in Nigeria for men who present with prostate pathology.[26,27,34] Indwelling catheter for urinary retention, transurethral resection and open prostatecomy for BPH, orchidectomy and radical prostatectomy for the management of prostate cancer are well documented in hospital studies.[5,7, 27,35,36] Patients accept prostate biopsy in the hospital setting as part of the management for their illness for which they sorted treatment, most of the time with very severe symptoms and advanced disease. This is contrary to our experience in this community setting, a situation that involves 'healthy' men who did not present with symptoms and do not realize that they may have prostate pathology. This poor response to prostate biopsy that is not specific to this group of Nigerians is bothersome and warrants careful attention.

The men in this study had in-depth group prostate health education by the PI and one-on-one counseling by the clinic doctor about screening for prostate disease and the need for a prostate biopsy in the event of an abnormally high PSA as part of the 'informed consent' process. In addition, the community nurse who hand-delivered results in the form of a health certificate encouraged the men with abnormal results to see the clinic doctor for further counseling regarding their results. The men who presented after receiving their abnormal results were then counseled about the necessity and safety of the prostate biopsy procedure. A second home visit was paid to men who were yet to consult the doctor about their abnormal results for the same purpose. Thus men with abnormal PSA received prostate counseling at least three times and their non-compliance

cannot be attributed to lack of knowledge about the procedure. The study surgeon from previous experience with surgical patients noted 'irrational morbid fear of impotence following procedures around the ano-rectum' as a probably major reason for the default.

The second constraint could be financial as these men pay out-of-pocket for their health and there is no national health insurance scheme in the country. Only 23(15.2%) work with a company that pays for their medical care. In the three-tier health referral system, patients seen in a primary health center are referred to specialists in the secondary or tertiary health institutions in an urban town. The study therefore arranged to reimburse participants for transportation to the teaching hospital and waive the fee for the prostate biopsy procedure. The study participants however had to pay the hospital registration fee so as not to set precedence. It is possible that some of the men could not afford or did not want to spend the time and money to travel to the teaching hospital for this procedure, as they felt 'healthy'.

Another reason for non-compliance proposed by the clinic doctor is not only fear of the procedure but more importantly fear of the diagnosis (cancer fatalism). Fear of the procedure could have been increased because of the emphasis placed on 'all possible risks' of the procedure such as hemorrhage, infection and impotence enumerated on the informed consent as required by the institutional review board (IRB). It is possible that they do not want to take any chances with a procedure in their 'healthy' state. As the study is not funded to pay for treatment of prostate cancer, inability to pay for treatment in case of a positive diagnosis can be a true deterrent for having a prostate biopsy, as some people will rather not know about a diagnosis if they cannot afford treatment.

There is need to confirm these findings in a larger study especially since it is known that African-Americans, who have their origins in Africa, record the highest prostate cancer incidence in

the world and previous reports have reported very low rates of prostate cancer in this region. The proposal for extension of the study will include training of the personnel in the local health center to conduct extensive community based cancer education campaign that will include prostate cancer. The campaign will include audio-visual presentations and question-and-answer discussion sessions with the village council of chiefs and other groups of men and women, the distribution of prostate cancer information materials and in depth personalized discussion sessions at the neighborhood level during home visits by a team that will include a doctor, a community nurse and a community health worker.

CONCLUSION:

There is a 15.7% prevalence rate of PSA ≥4ng/ml among men 50 years and older in this rural previously unscreened African population with little or no urbanization or Westernization. This rate is similar to that reported from other previously unscreened populations in developed countries. Although there are several causes of elevated PSA there is no evidence of prostatitis in this population. Age and enlarged prostate are the main correlates of elevated PSA. This finding therefore suggests that prostate cancer may be more common in Sub-Saharan African blacks contrary to earlier reports. The fear of prostate biopsy and fear of a diagnosis of prostate cancer irrespective of educational status is an important finding that deserves careful attention. There is need to confirm these findings in a larger study, initiate a prostate cancer awareness campaign in the area emphasizing the need and safety of prostate biopsy and secure prostate biopsy from the high risk sub-population with abnormal PSA ≥4ng/ml and/or abnormal prostate on DRE and determine the prevalence of prostate cancer in this population.

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Table 1. Mean and Median PSA by Demographic Characteristics of the Study Population in Rural Nigeria

	N(%) N=151	PSAng./ml. Mean (Median)
Age		
< 50	56(37.1)	1.17 (0.60)
50-59	34(22.5)	1.57 (0.55)
60-69	32(21.2)	2.05 (0.90)
70-79	16(10.6)	5.69 (1.25)
≥ 80	8(5.3)	13.75 (4.45)
Not Recorded	5(3.3)	0.55 (0.60)
Educational Status		
0 – 6 Years	61(40.4)	4.60 (1.10)
6 – 9 Years	60(39.7)	1.74 (0.60)
High School	16(10.6)	0.75 (0.55)
Technical Training	10(6.6)	0.62 (0.60)
College / Graduate	4(2.7)	1.43 (1.80)
Marital Status		
Single	2 (1.3)	*
Married (One Wife)	94(62.3)	1.92(0.70)
Married (> 1 Wife)	47(31.1)	3.97(0.75)
Separated/Divorced	6(4.0)	0.96(0.60)
Widowed	2(1.3)	*
Alcohol Use		
Regularly	56(37.1)	2.38(0.70)
Occasionally	68(45.0)	1.92(0.70)
None	24(15.9)	5.90(0.60)
Tobacco Use		
Cigarettes	65(43.0)	1.57(0.70)
Sniff	26(17.2)	2.48(0.70)
Chew	1	*
Cigar	1	*
None	52(34.4)	4.35(1.00)

* Mean (median) not calculated for n <4

Table 2: PSA Distribution of Rural Nigerian Men by Age Group

PSA (ng./ml.)	Age Group N (%)				Total N(%)
	< 60	60 - 69	70 - 79	≥ 80	
0.0-2.4	75(90.4)	20(69.0)	9(56.2)	2(25.0)	106(77.9)
2.5-3.9	5(6.0)	6(20.7)	3(18.8)	2(25.0)	16(11.8)
4.0-9.9	0(0.0)	2(6.9)	1(6.2)	2(25.0)	5(3.7)
≥10.0	3(3.6)	1(3.4)	3(18.8)	2(25.0)	9(6.6)
Total	83	29	16	8	136
%	61.0	21.3	11.8	5.9	100.0

Table 3.

Distribution Pattern of Prostate Status by DRE of Rural Nigerian Men by Age Group

DRE	Age Group N (%)				Total N(%)
	< 60	60 - 69	70 - 79	≥ 80	
Normal	66(83.5)	19(65.5)	5(35.7)	2(25.0)	92(70.2)
Enlarged No Symptom	10(12.7)	7(24.1)	6(42.9)	1(12.5)	24(18.3)
Enlarged With Symptoms	3(3.8)	3(10.3)	3(21.4)	3(37.5)	12(9.2)
Nodular (suspicious of cancer)	0	0	0	2(25.0)	2(1.5)
Total	79	29	14	8	131
%	60.3	22.1	10.7	6.1	100.0

Table 4 PSA Distribution by Prostate Status by DRE of Rural Nigerian Men.

PSA (ng./ml.)	Prostate Status (DRE) N (%) Normal	Enlarged No Symptom	Enlarged With Symptoms	Nodular (Suspicious of Cancer)	Total N(%)
0.0-2.4	79(84.9)	14(58.3)	3(25.0)	1(50.0)	97(77.6)
2.5-3.9	6(6.5)	7(29.2)	2(16.7)	0	15(12.0)
4.0-9.9	1(1.1)	1(4.2)	2(16.7)	0	4(3.2)
≥10.0	2(2.2)	2(8.3)	4(33.3)	1(50.0)	9(7.2)
N	88	24	11	2	125
%	70.4	19.2	8.8	1.6	100.0

Anthropometric and Body Fat Predictors of Elevated Prostate Specific Antigen among Rural and Urban Nigerians: A Population-Based Study

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Abstract:

In-person interviews were conducted between 1999 and 2001 in a population-based, cross-sectional study of rural and urban Southern Nigerians, 40 years and older, to investigate the role of body fat in prostate cancer risk as a step towards understanding the rapid increase in prostate cancer incidence in this once designated low incidence region. Height, weight, waist, hip, mid-arm circumference and skin fold thickness over the biceps, triceps and subscapular area were measured in light cotton clothes. Venous blood sample was drawn and stored at -20^0C until shipped on dry ice for PSA analysis. Association between anthropometrics and PSA was conducted using Spearman's correlation coefficient and odds ratio (OR) from multivariate logistic regression. Analysis was limited to 281(84%) men who completed the protocol with a mean age was 56.9±13.5. Rural men recorded lower BMI, 22.9 vs 24.7, $p<0.002$ and lower skin fold thickness than urban men but WHR was similar, 0.92. PSA correlated directly with age, $r=0.360$, $p<0.0001$ and negatively with height, $r=-0.136$, $p<0.023$. WHR predicted elevated PSA $\geq$ 4ngs/ml after adjusting for age and enlarged prostate, OR 3.04, 95% CI = 1.13 - 8.15, $p< 0.01$, but height, BMI and skin fold thickness did not. There is need to prospectively investigate the role of body fat, selected micronutrients and hormones in prostate cancer risk among distinct socio-economic cohorts with differential dietary, physical activity and body fat history and pattern in this and other Western populations that record much higher rates of central obesity and prostate cancer incidence.

Introduction

Obesity is associated with several diseases such as hypertension, diabetes, heart disease and several forms of cancer including prostate cancer, and has become a serious problem in the United States of America, particularly among the black population (1,2). Obesity and other related diseases such as hypertension and cancer have now attained epidemic proportions in some African countries (3) such that prostate cancer has become the number one cancer among Nigerian men (4). The proportion of cancers attributable to excess body weight was estimated by meta analysis at 5%, ranging from 2.1% to 8.8% of all cancers in men and women in European countries. The association between excess body fat and cancer risk is strongest for cancer of the kidney and gallbladder, colon, endometrium and breast (5). There is however growing evidence of increased risk for prostate cancer from excess body weight both in white and black men in America (2). While obesity defined as body mass index (BMI) ≥ 30 kg/m^2, after adjusting for age, was only weakly associated with prostate cancer risk (6), death from prostate cancer was significantly higher among obese men and the tallest men. The overall decreased survival among obese men may have contributed to this finding (7). A more resent study reported that obesity (BMI ≥ 35 kg/m^2) was associated with higher grade tumors and worse outcome following radical prostatectomy and that black men were significantly more likely to be obese than all other men (8). Making the role of obesity in prostate cancer epidemiology particularly important for men of African ancestry. The connection between obesity and prostate cancer is not an unexpected finding as there is a strong endocrine component of body fat distribution and hormonally dependent cancers in both men and women.

Studies investigating the role of body fat distribution in prostate cancer risk have been conducted in different age groups, using a variety of study designs, varying lengths of follow-up and methods of data analysis. Some of the studies looked at the risk related to the incidence of prostate cancer in

general while others limited their findings to the risk for aggressive prostate cancer or fatal prostate cancer. Reported findings have therefore been inconsistent regarding the role of body fat in the etiology of prostate cancer (9). Abdominal adiposity measured as waist-to-hip (WHR) is a distinct measure of body fat distribution that is independent of BMI and is also under the influence of hormones, diet and inactivity. WHR has been reported to be associated with clinical prostate cancer with a three-fold increased risk between the lowest and the highest quartile of WHR >0.92, in a case-control study of a very lean Chinese population with mean BMI of 21.9 and a rapidly increasing incidence rate for prostate cancer. Adult height, weight, BMI and pre-adult BMI were not associated with prostate cancer risk in this population (10).

A cohort study in the Netherlands followed up over 58,000 men and did not find any clear association between prostate cancer risk and adult anthropometric parameters. They however found an increasing trend for prostate cancer risk for pre-adult BMI groups at age 20, starting with BMI less than 19 up to BMI greater than 25. BMI gain from age 20 to baseline at the onset of this study showed an inverse trend in risk that disappeared after adjusting for BMI at age 20, emphasizing that the mechanism for the development of prostate cancer could have been affected by body composition in young adulthood and may not be influenced by adult anthropometry (11). Cohort studies from the United States of America continue to report conflicting results regarding pre-adult BMI. The Health Professional Follow-up Study of 33,000 men concluded that pre-adult obesity is prospectively related to a lower risk of advanced prostate cancer. They also found that neither adult BMI nor waist and hip circumferences were appreciably related to risk of prostate cancer (12). Pre-adult BMI at 18 years and adult weight in a relatively smaller American study of about 9,000 men did not relate to the risk of prostate cancer (13).

Although height is genetically determined, it is also an indicator of nutritional factors of early life mediated through the endocrine system. Some studies have reported that pre-adult tallness (12) and adult height (14) are risk factors for aggressive and metastatic prostate cancer. Other studies in the USA (7,15), China (10) and Norway (16) concluded that height alone was not related to the risk of fatal prostate cancer. The inconsistency regarding the role of pre-adult and adult obesity in prostate cancer etiology in conjunction with other risk factors such as physical inactivity is reflected in the literature. Case-control (17,18) and cohort (19-23) studies reported BMI as a modest but important anthropometric risk factor for prostate cancer incidence and mortality but did not document information on WHR. Several studies have not found BMI (10-13,16,24-26) or WHR (25,27) to predict prostate cancer risk. A study that looked at fat distribution, skeletal structure and musculature did not find skin fold thickness to be a risk for prostate cancer but reported that prostate cancer cases exhibited a propensity toward a slight upper body skeleton, a possible benchmark of past nutritional and/or hormonal status (28).

Few reports of detailed epidemiological studies of anthropometric correlates of prostate cancer from Africa appear in the literature. Prostate cancer studies from Nigeria describe the men to be of average build, low-normal BMI range, and found no relationship between prostate cancer and BMI (4,29), but a study from Cameroon concluded that there might be an association between obesity and prostatic tumor (30). A similar association was reported in a study of South African blacks where they alluded to increase in prostate cancer incidence with urbanization and prosperity, with a possible dietary role for Western as compared to Third World diet (31,32).

Since anthropometry is an expression of complex interaction of both genetic and environmental factors and a relatively inexpensive method of investigating human body composition (33), this study is designed to investigate the anthropometric and body fat correlates of elevated prostate

specific antigen (PSA) among a sample of apparently healthy men from selected rural and urban communities in southern Nigerian. This cross-sectional study is a necessary first step in the investigation of the role of body fat in prostate cancer risk in this population as routinely measured anthropometry is limited to weight and height among patients presenting in the hospital for disease management. While current BMI can be studied among sick persons presenting in the hospital for treatment, it will not be possible to investigate pre-adult or adult adiposity of healthy people, as they do not usually present for routine medical examination. The specific objectives of this study are to measure anthropometric indices of body fat such as weight, skin fold thickness, waist and hip girth, compute WHR and BMI, measure serum PSA among community based rural and urban men in Nigeria, examine the association between these anthropometric indices of body fat and PSA levels and determine the anthropometric predictors of elevated PSA in this population. Participants recruited into this study and the data collected will be useful in developing a cohort study in this population.

Materials and Methods

Study population. This study was conducted in two rural and two urban communities in Edo and Delta states of Southern Nigeria. The procedure for recruiting and consenting participants and the process for collecting and processing blood samples have been described (34). Trained interviewers collected general demographic information including history of urinary symptoms, family history of prostate and other cancers and anthropometric measurements. Participants wore light cotton clothes while being measured. Weight (WT) was measured in kilograms using a digital scale. Height (HT), waist (WST) at the umbilicus and hips at the highest protrusion of the buttocks with feet together were measured with a measuring tape in centimeters. Body mass index (BMI) was computed as

weight in kilograms divided by height in meters squared, and waist-to-hip ratio (WHR) was computed as waist in centimeters divided by hips in centimeters. With sleeves rolled up, arm flexed and resting on the chest, mid-arm circumference (MAC), biceps (BI) and triceps (TRI) skin fold thickness of the right arm, and sub-scapular (SUB) skin fold thickness below the right scapular were measured in millimeters using the Slim Guide skin fold calipers. Prostate specific antigen (PSA) analysis was conducted in a commercial laboratory in the United States of America, using microparticles enzyme immunoassay technology (35).

Statistical analysis. The study population was dichotomized by occupation (farmers and non-farmers), place of residency (rural and urban) and age using the cut-point of 55 years, which is the current age for compulsory public service retirement in Nigeria and median age for the study population. Median anthropometry was compared across age, occupation and residency groups using non-parametric Mann-Whitney test. Mean PSA was tested for linearity across tertiles of BMI, WHR, obesity status, and skin fold thickness. Multivariate logistic regression was used to determine predictors of elevated PSA $\geq$ 4ng/ml, controlling for age and enlarged prostate size on digital rectal examination (DRE). The statistical program for the social sciences (SPSS 12.0) was used for data collection and basic analysis and SAS 8.2 was utilized for multivariate logistic regression analysis.

Results

Two hundred and eighty-one (84.1%) of the 334 volunteers completed the study protocol. Thirty-eight men who did not allow blood draw and 15 men who did not complete anthropometric measurements were excluded from further analysis. There were 178(63.3%) rural and 103(36.7%) urban dwellers with similar age distribution that ranged from 40 –100 years, mean 56.9 $\pm$ 13.5

years. Men in the urban community were more educated, 17% (17/103) with college degrees as compared to 2.2% (4/178) rural men and the rates for men with less than 6 years formal education was 9.0% (9/103) and 44.4% (79/178) respectively. There was statistically significant difference in their occupational status, 11.0% (11/103) vs. 73.0% (130/178) were farmers among urban and rural men respectively, and 50.5% (52/103) urban men as compared to 11.2% (20/178) rural men were retired or not working, $p< 0.0001$. The rural men were smaller than their urban counterparts with BMI, 22.9 vs 24.7, $p<0.001$ and overweight/obesity rate of 24.7% to 45.3%, $p<0.001$. All other anthropometric measures significant lower in the rural men except WHR that was similar for both groups, 0.92.

The rates for elevated PSA ≥ 4ng/ml was 20.8% (30/144) for men 55 years and older (older men) and 0.8% (1/133) for those under 55 years (younger men). The proportion of men with elevated PSA ≥ 4ng/ml was 12.6% (13/103) and 10.1% (18/178) for urban and rural men respectively, and among the older men the equivalent rates were 24.1% (13/54) and 18.9% (17/90) and PSA significantly correlated with age only among the older men, $r=0.29$, $p<0.0001$. The urban men recorded statistically significant higher proportion of enlarged prostate on DRE, (40.8% (42/103) vs (28.1% (50/178) (Table 1). The rural-urban rate difference for enlarged prostate was statistically significant only for the younger men, 8.9% (7/79) to 33.3% (14/42), $p<0.001$, but not the older men, 50.6% (44/87) to 62.5% (30/48). The prevalence of enlarged prostate was statistically higher among older men compared to the younger men, 54.8% (74/135) vs 17.4% (21/121), $p<0.0001$

The older men were shorter than the younger men, median height 165.7 to 167.1, $p<0.01$, had a higher WHR, median 0.93 to 0.91, $p<0.0001$ and comparable BMI, median 23.0 to 22.7. The non-farmers consistently recorded statistically higher measurements than the farmers with a height of 168.8cms to 165.6cms, $p<0.0001$ and the pattern was the same for the younger and older groups.

WHR was similar for farmers and non-farmers within both age groups, 0.91 vs 0.90 among the younger men and 0.93 vs 0.94 among the older men respectively. The older farmers were the leanest with BMI of 22.2, MAC 27.9cms but WHR 0.93. The younger farmers had a BMI of 22.9, MAC 29.2cms and WHR 0.90. The younger non-farmers were the middle level workers, low-income artisans and semiskilled workers with a BMI of 23.8, MAC 30.2cms and WHR 0.91. The older non-farmers were the local landlords, contractors and owners of small businesses, with higher BMI of 27, MAC 31.4cms and WHR of 0.97 (Table 2).

Age dichotomized at the median, 55 years, was a significant predictor of elevated PSA and enlarged prostate, OR 34.74 (95% CI 4.66, 258.75), $p<0.001$ and OR 5.78 (95% CI 3.23, 10.32), $p<0.001$ respectively. The anthropometric correlates of elevated PSA were different from those of enlarged prostate and the pattern was similar for rural and urban men. The significant anthropometric predictors of elevated PSA were biceps skin fold, OR 3.04 (95% CI 1.03 – 9.01) and WHR, OR 3.11 (95% CI 1.33 – 7.26), and height, OR 0.36 (95% CI 0.16 – 0.82). WHR remained a significant predictor of elevated PSA among men 55 years and older, OR 2.67 (95% CI 1.12 – 6.38). Weight and MAC were negative predictors of enlarged prostate, OR 0.45 (0.23 – 0.91) and OR 0.40 (0.20 – 0.81). This pattern was retained among the older men, OR 0.45 (0.23-0.91) and OR 0.40 (0.20-0.81) respectively (Tables 3). After adjusting for age and enlarged prostate size, WHR remained a significant predictor of elevated PSA, OR 3.04 (95% CI 1.13, 8.15) (Table 4). The incidence of elevated PSA among men in the lowest, middle and third WHR tertiles was 13.5%, 18.0% and 34.9%, $p<0.0001$. Men in the third WHR tertile recorded increased risk for elevated PSA in comparison to those in the lower WHR tertile with an OR of 3.20 (1.06, 9.64) after adjusting for age and enlarged prostate (Table 5).

Educational status, farming and income level did not predicted elevated PSA and the risk for elevated PSA for the older farmers and non-farmers was 20.0% to 23.0% respectively. None of the study participants reported a family history of prostate cancer.

Discussion

This community-based study addressed anthropometric prostate cancer risk in apparently healthy Sub-Saharan African men, before the onset of disease or at the pre-diagnostic or latent stage. The study shows that central adiposity, not BMI, skin fold thickness or height, is associated with risk for elevated PSA. Genetic factors, pre-adult and adult body fat have consistently been reported to affect prostate cancer risk. However, early life hormonal milieu as expressed in maximum height attained was not an important predictor of elevated PSA in this population. This is in line with the finding that height alone was not related to the risk of prostate cancer deaths in studies conducted in the United States of America (7,15).

Results from case-control and cross-sectional studies show only modest or no association between prostate cancer risk and measures of obesity such as BMI or WHR probably because these measures have already undergone modification either as a result of the disease process or behavior change based on the understanding that weight reduction is beneficial for cancer prognosis. Patients in these studies include those with clinical prostate cancer (21), prostate cancer stage T2 and greater (25) and aggressive prostate cancer (10). Some cohort studies recruit and follow-up patients for several years after diagnosis as reflected in the person-years reported (22). This study was and participants with elevated PSA can only be diagnosed with prostate cancer on the basis findings for the prostate biopsy.

Cohort studies that recorded anthropometry before the onset of disease did show obesity, BMI, height and other aspects of body size to be risk factors for prostate cancer incidence and mortality, especially when measurements were collected as part of a study protocol by trained staff. (7,19,23). That the association between body size and prostate cancer risk is stronger for those who were diagnosed 11 years after the study was initiated underscores the importance of studying baseline measures long before the onset of disease, before the disease process begins to modify body fat (36). This community-based study has addressed prostate cancer risk in apparently healthy men, before the onset of disease or at the pre-diagnostic or latent stage.

Several reasons can account for prospective cohort studies that fail to demonstrate any association between measures of obesity and prostate cancer. If the mean age of the studied group is over 65 years (13) then the prostate cancer process could have started 10 or more years prior to study recruitment and would have had some effect on body size measurements. While several studies reported pre-adult BMI that is more related to lean body mass than obesity, there was very little information on pre-adult WHR (11,16). Self-reported physical measurements and those collected from multi-center routine clinical settings (26) may lack the accuracy of research protocols and their associations with disease risk may be distorted.

Since age and prostate enlargement are the strongest correlates of PSA, the odds ratio for the anthropometric and other predictors of prostate cancer were adjusted for both variables. About three quarters of the men with enlarged prostate had moderately enlarged prostate on DRE, and only a quarter of them complained of related urological symptoms. Since the anthropometric correlates of enlarged prostate were different from those of elevated PSA in this study and benign prostatic hyperplasia does not preclude risk for prostate cancer, analysis was combined for all men regardless of prostate size on DRE. Central adiposity, not BMI or skin fold thickness, is associated with risk

for elevated PSA in this population. The confounding role of diet, hormones and body fat in cancer etiology cannot be over emphasized (37).

The two-way rural-urban drift between rural farming communities located outside the suburb of urban cities is determined by socio-economic factors. Young men from lower socio-economic status (SES) may not have the resources to move and therefore remain in the rural setting as peasant farmers. The pensioners in the rural community include men from a wide spectrum of economic backgrounds, ranging from those who returned home to farming and the simple rural lifestyle from very low paying jobs, to those who have earned enough to retire into a comfortable and leisure lifestyle, earning additional income from small businesses, contract jobs and renting of farm land and housing. There are other important none anthropometric risk factors of prostate cancer that have not been addressed in this study (38).

Physical inactivity has been associated with the risk for cancer (39). The only evidence of leisure physical activity for adults in the study urban community was golf and racket sports and this was restricted to the elites, very few of who are represented in this study population. There was no evidence of leisure physical activity for adults in the rural community making farming and cycling the main forms of occupation-related physical activity. Although this study did not specifically address physical activity, farming as compared to non-farming jobs can be used as an index of increased physical activity. Cross stratification by farming status and age cut-point of 55 years provided four socio-economic cohorts with possible differential developmental history and body size patterns. The older farmers being the leanest with BMI 22.2, MAC 27.9 cms and WHR 0.93, followed by the younger farmers with BMI 22.9, MAC 29.2 cms and WHR 0.90. The non-farmers were bigger and taller than the farmers, indicating relatively higher SES, better nutrition and less physical activity, both in the past and the present. The younger non-farmers had BMI 23.8, MAC

30.2 cms and WHR 0.91 and the older non-farmers who were more affluent were the largest with BMI 27.0, MAC 31.4 cms and WHR 0.97. The older retired non-farmers lacked physical activity in the past and in the present and their recently acquired high body fat, skin fold thickness and WHR has not translated into appreciable increased risk for elevated PSA. The older farmers from a lower SES background with past and present higher levels of physical activity and lower BMI were not protect from the risk of elevated PSA in the presence of moderately high WHR. It would appear that the risk for elevated PSA associated with increased central adiposity was established much earlier in life before the age of 40 years. Central adiposity in early adulthood may be more important in the risk for elevated PSA than central adiposity acquired later on in adulthood. This is in line with the finding that pre-adult body fat is a risk for prostate cancer (11,40,41). That body fat predicts prostate cancer risk in such a lean population with low prostate cancer incidence is serious implications for populations with high prevalence of obesity and prostate. Just as severe obesity explains the relative disadvantage in breast cancer outcomes for African American women (42), it is also important for prostate cancer outcome among African American men (8), warranting further research into the hormonal, metabolic and other mechanisms of action especially as African American men record increasing prevalence of overweight, from 53.9% in 1960 to 71.3% in 2000 (43) and an incidence for prostate cancer remains higher than their white counterparts at 275.9/100,000 (44).

This study, although limited by a small sample size and the current absence of prostate biopsy follow-up information on the men with elevated PSA, confirms the feasibility of a large community-based prostate cancer cohort study in Nigeria, a Sub-Saharan Africa country currently experiencing an increase in the incidence of prostate cancer. One of the study strengths is that comparison of physical measurements is between apparently healthy men and those who may have

latent or early stage undiagnosed prostate cancer that has not adversely affected their body size pattern. The fact that none of the study participants reported a family history of prostate cancer indicates the overall lack of awareness of this disease in this population. It is also probable that participants were not aware of the cause of death of their relatives or that men died with undiagnosed prostate cancer. A cohort study in this population where routine PSA screening is not yet an established practice will provide the opportunity to adequately study the anthropometric predictors of prostate cancer among men with elevated PSA stratified by prostate size, include an acceptable strategy to encourage men to have a prostate biopsy if they have elevated PSA and/or abnormal prostate on DRE, measure body fat with more precision using the more accurate impedance technology, determine the role of selected dietary micronutrients in the etiology of prostate cancer and explore the hormonal and insulin-related mechanisms that may affect prostate cancer risk in this very lean understudied population. Long-term research plans will include identifying and recruiting families with multiple cases of prostate cancer for more detailed genetic studies.

Conclusion

Up to 11.0% of a lean moderate to high physically active rural and urban African men have elevated PSA above 4.0 ng/ml suspicious of prostate cancer that was only predicted by central adiposity (WHR). This is consistent with the current implication of hormonal or insulin-related mechanism in the etiology of prostate cancer. Additional research is needed to confirm this finding in a larger prospective study in this population with increasing incidence of prostate cancer and in transition from a lean body structure to the moderate obesity of the more affluent western populations. Socio-economically stratified cohorts from the same genetic pool but with distinct

body size patterns resulting from differential dietary and physical activity history have been identified and can be followed up to investigate the role of body fat in prostate cancer risk. Precise body fat measurements by the impedance technique, genetic, dietary and physical activity information need to be collected to determine their interactions in the underlying hormonal mechanism operational in the pathogenesis of prostate cancer.

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Table 1: Demographic Characteristics, PSA and DRE Distribution of Rural and Urban Nigerian Men

	RURAL 178 (63.3%)	URBAN 103 (36.7%)	TOTAL 281	
Characteristics			N	%
Age ns				
40-49	64(36.6)	35(34.3)	99	35.7
50-59	44(25.1)	26(25.5)	70	25.3
60-69	36(20.6)	22(21.6)	58	20.9
70-79	21(12.0)	12(11.8)	33	11.9
≥80	10(5.7)	7(6.9)	17	6.1
Not Recorded	3 --	1 --	4	--
Mean Age	56.7 ± 14.1	57.4 ± 12.5	56.9 ± 13.5	
Education p<0.0001				
< 6 years	79(44.6)	9(9.0)	88	31.8
6 – 12 years	81(45.8)	61(61.0)	142	51.3
> 12 years	17(9.6)	30(30.0)	47	17.0
Not Recorded	1 --	3 --	4	--
Occupation p<0.0001				
Farming	130(73.9)	11(11.0)	141	51.1
Semi-/Skilled	20(11.4)	38(38.0)	58	21.0
Teaching/Jr.Admin	22(12.5)	34(34.0)	56	20.3
Manager/Professional	4(2.3)	17(17.0)	21	7.6
Not Recorded	2 --	3 --	5	--
Obesity p<0.001				
Underweight	17(9.8)	3(3.2)	20	7.4
Normal	113(64.9)	49(51.6)	162	60.2
Overweight	38(21.8)	29(30.5)	67	24.9
Obese Class I	5(2.9)	11(11.6)	16	5.9
Obese Class II	1(0.6)	3(3.2)		4
Not recorded	4 --	8 --		.5
			12	--
PSA (ng/ml) ns				
0 - 2.4	143(80.3)	83(80.6)	226	80.4
2.5 - 3.9	17(9.6)	7(6.8)	24	8.5
4.0 - 9.9	6(3.4)	7(6.8)	13	4.6
10.0-49.9	11(6.2)	3(2.9)	14	5.0
≥ 50.0	1(0.6)	3(2.9)	4	1.4
Prostate Size p<0.007				
Normal	116(65.2)	46(44.7)	162	57.7
Enlarged	52(29.2)	44(42.7)	96	34.1
Refused / Not Done	10(5.6)	13(12.6)	23	8.2

Table 2 Mean Anthropometric Measurements by Occupation for Younger and Older Cohort of Rural & Urban Nigerian Men

	Mean (sd)			
	< 55 YEARS		≥ 55 YEARS	
Measures	Farmers (60)	Non-Farmers (73)	Farmers (80)	Non-Farmers (61)
Waist (cm)	81.0 (9.5)	85.2 (10.3)*	83.3 (8.3)	90.7 (14.7)***
Hip (cm)	89.8 (7.1)	93.5 (8.8)*	88.9 (6.4)	96.7 (11.6)***
MAC (cm)	28.0 (3.1)	29.4 (3.2)*	27.6 (2.7)	29.7 (3.6)***
Height (cm)	165.2 (6.9)	170.1 (7.1) ***	164.4 (6.6)	167.3 (8.0) *
Weight (kg)	62.4 (10.7)	69.1 (12.6)**	59.9 (8.9)	71.9 (16.1)***
Biceps (mm)	4.5 (2.2)	5.2 (2.6)	4.5 (1.8)	6.7 (3.3)***
Triceps (mm)	7.4 (3.7)	9.1 (4.8)*	7.9 (3.7)	10.9 (4.2)***
Subscapular (mm)	11.9 (5.5)	13.6 (6.1)	11.7 (4.8)	17.0 (7.1)***
BMI	22.9 (3.6)	23.8 (3.8)	22.2 (3.0)	25.6 (5.1)***
WHR	0.90 (0.08)	0.91 (0.06)	0.94 (0.05)	0.93 (0.07)
Age	46.0 (4.5)	45.9 (4.2)	68.2 (12.1)	65.8 (8.6)
% Abnormal PSA	1(1.7%)	0(0.0%)	16(20.0%)	14(23.0%)

* $p < 0.05$ ** $p < 0.001$ *** $p < 0.0001$

Table 3. Anthropometric predictor factors of elevated PSA and enlarged prostate in rural and urban Nigerian men.

	Mean (Standard Deviation)		Crude Odds Ratio (95% CI)	
Predictors	Cases	Controls	Elevated PSA	Enlarged Prostate
Weight	66.19 (19.59)	65.61 (12.06)	0.72 (0.34, 1.55)	0.42 (0.25, 0.71) ***
Height	165.41 (7.30)	166.95 (7.48)	0.36 (0.16, 0.82)**	0.94 (0.57, 1.57)
Waist	89.25 (14.32)	84.56 (10.64)	1.15 (0.54, 2.46)	1.21 (0.73, 2.02)
Hip	93.07 (11.64)	91.97 (8.73)	0.98 (0.46, 2.08)	0.76 (0.46, 1,28)
MAC	28.53 (4.24)	28.64 (3.18)	0.68 (0.32, 1.46)	0.55 (0.33, 0.92) *
Bicep	5.97 (3.11)	5.07 (2.55)	3.04 (1.03, 9.01) *	1.52 (0.84, 2.72)
Tricep	10.18 (4.66)	8.63 (4.31)	1.61 (0.75, 3.47)	1.14 (0.68, 1.92)
Subscapular	15.00 (7.75)	13.24 (5.95)	1.53 (0.71, 3.29)	1.03 (0.61, 1.73)
BMI	23.96 (5.52)	23.51 (3.86)	0.74 (0.34, 1.59)	0.82 (0.49, 1.36)
WHR	0.95 (0.63)	0.92 (0.65)	3.11 (1.33, 7.26) **	1.45 (0.87, 2.43)

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$

Table 4. Anthropometric predictor factors of elevated PSA among rural and urban Nigerian men: Odds Ratio adjusted for age and enlarged prostate.

Predictors	Crude Odds Ratio (95% CI) OR Adjusted for Age	OR Adjusted for Age and Enlarged Prostate
Weight	1.03 (0.44,2.39)	1.15 (0.45,2.89)
Height	0.45 (0.19, 1.08)	0.56 (0.22, 1.39)
Waist	1.36 (0.59, 3.16)	1.01 (0.41, 2.45)
Hip	1.04 (0.45, 2.39)	1.14 (0.47, 2.78)
MAC	0.90 (0.39, 2.08)	1.19 (0.48, 2.98)
Bicep	3.04 (0.85,10.9)	2.97 (0.77,11.5)
Tricep	1.73 (0.73, 4.09)	1.62 (0.65,4.03)
Subscapular	1.74 (0.73, 4.13)	1.47 (0.59, 3.65)
BMI	1.00 (0.43, 2.31)	0.86 (0.35, 2.13)
WHR	2.76 (1.10, 6.92) **	3.04 (1.13, 8.15) **

** $p < 0.01$

Table 5: Waist-Hip-Ratio and other Categorical Predictors of Elevated PSA among Rural and Urban Nigerians: Odds Ratio Adjusted for Age and Enlarged Prostate.

Predictor	Cases (Elevated PSA)	Controls	Odds Ratio	95% CI	p-val
Age					
< 65	13 (41.9)	189 (76.8)	1.00		
≥ 65	18 (58.1)	57 (23.2)	4.59	2.12, 9.94	0.0001
Waist-hip-ratio					
0.66 – 0.90	6 (20.0)	89 (36.6)	1.00		
0.90 – 0.95	8 (26.7)	88 (36.2)	1.15	0.31, 4.22	0.43
0.95 – 1.17	16 (53.3)	66 (27.2)	3.20	1.06, 9.64	0.02
Obesity (BMI > 25)					
No	14 (56.0)	148 (66.1)	1.00		
Yes	11 (44.0)	76 (33.9)	1.53	0.66, 3.53	0.32
Income					
Low	21 (77.8)	146 (65.8)	1.00		
Medium	1 (3.7)	40 (18.0)	0.40	0.05, 3.42	0.25
High	5 (18.5)	36 (16.2)	2.01	0.71, 5.70	0.10
Occupation					
All Others	14 (45.2)	121 (49.4)	1.00		
Farming	17 (54.8)	124 (50.6)	0.72	0.29, 1.78	0.66